Correlation between Blood Ethylenethiourea and Thyroid Gland Disorders among Banana Plantation Workers in the Philippines

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Ethylenebisdithiocarbamates (EBDCs) are metabolized into ethylenethiourea (ETU), a possible human carcinogen and an antithyroid compound. In this study our goal was to correlate ETU levels with the incidence of thyroid gland disorders among banana plantation workers exposed to EBDC. We randomly selected 57 directly exposed workers and 31 indirectly exposed workers from four banana plantations and 43 workers from an organic farm; all subjects underwent complete medical examinations and laboratory tests. Results showed a higher mean thyroid-stimulating hormone measurement among exposed workers compared with the control group, although the levels were well within normal range. Nine of the exposed farmers had abnormal thyroid ultrasound findings, consisting mostly of solitary nodules, compared with three among the control group. Analysis of variance showed significantly different blood ETU levels among the directly exposed, indirectly exposed, and control groups ($p < 0.001$), but ETU levels in urine were not significantly different ($p = 0.10$). Environmental ETU levels were below the U.S. Environmental Protection Agency remediation levels. Among farmers with solitary thyroid nodules, we found a very good direct correlation between the size of the nodule and blood ETU level. In this study we showed that blood ETU is a more reliable biomarker for EBDC exposure than urinary ETU; therefore, the determination of blood ETU should be part of medical surveillance efforts among workers exposed to EBDC to detect occurrences of thyroid gland disorders. ***Key words:*** **banana plantations, biologic monitoring, blood ethylenethiourea, environmental monitoring, ethylenebisdithiocarbamate exposure, thyroid gland disorders.** ***Environ Health Perspect*** **112:42–45 (2004). doi:10.1289/ehp.6499 available via** ***http://dx.doi.org/*** **[Online 22 October 2003]**

Ethylenebisdithiocarbamates (EBDCs) such as maneb and mancozeb have been extensively used in Philippine banana plantations for the past 40 years. These fungicides are applied through aerial or backpack spraying. EBDCs (zineb and maneb) are broken down into ethylenethiourea (ETU), which is a Type IIB carcinogen and an antithyroid compound [International Agency for Research on Cancer (IARC) 1991]. Furthermore, some ethylenebisdithiocarbamates contain ETU in their formulated products.

Animal studies using several mammalian species showed that ETU is rapidly absorbed from the gastrointestinal tract and cleared from the body. In one study (Kato et al. 1976), after only 5 min, ETU appeared in the blood of rats administered an oral dose of 100 mg ^{14}C-ETU/kg body weight. Within 48 hr, 82–99% of the oral dose was eliminated via urine and about 3% was eliminated via feces. Another study found that approximately 70% of an oral dose of ETU was eliminated in urine and 1% in feces (Newsome 1974; Ruddick et al. 1976). Comparable results were found for mice, whereas in monkeys 55% was eliminated via urine within 48 hr and < 1.5% was eliminated via feces (Allen et al. 1978). ETU and its metabolites have been found to have a half-life of about 28 hr in monkeys, 9–10 hr in rats, and 5 hr in mice [International Programme on Chemical Safety (IPCS) 1988]. Regarding the effects of dithiocarbamates on organ systems, studies done on exposed rats showed thyroid hyperplasia, which is largely reversible on cessation of exposure [Blackwell-Smith et al. 1953; Food and Agriculture Organization/World Health Organization (FAO/WHO) 1965, 1971; Seifter and Ehrich 1948]. Male rats given ziram, a metallobisdithiocarbamate, developed C-cell thyroid carcinoma (IPCS 1988).

In humans, urinary excretion of ETU among pesticide formulation workers varies according to the type of work. Aprea et al. (1998) reported that employees engaged in formulating 80% mancozeb excreted 65.3 µg ETU/g creatinine. Among those formulating 35% mancozeb, urinary excretion was 36.6 µg/g creatinine. Those engaged in maintenance and internal transport of materials excreted 10.3 µg/g creatinine (Aprea et al. 1998). Kurttio et al. (1990a, 1990b) reported an ETU excretion rate of 6–10 ng/hr among potato farmers during the first 60 hr after the cessation of exposure; the excretion rate diminished thereafter to 0.2 ng/hr over a 22-day observation period. The estimated half-life for eliminating ETU through the kidneys ranged from 32 to 100 hr (Kurttio et al. 1990a, 1990b). Studies on workers exposed to bisdithiocarbamates (thiram) in Russia revealed an increased incidence of thyroid gland disorders (7.6%) compared with a nonexposed group (1.0%), with one documented case of a malignant lesion of the thyroid (IARC 1991).

There are limited data in literature that indicate the sensitivity of ETU as a biomarker for EBDC exposure, and there are no reported studies that used blood ETU for monitoring. Furthermore, few epidemiologic studies have investigated the effects of EBDC exposure on the thyroid gland (Houeto et al. 1995; Smith 1984; Steenland et al. 1997; Brucker-Davis 1998). In the present cross-sectional study, we investigated the possible correlation between the levels of blood ETU and urinary ETU and the incidence of thyroid gland disorders among banana plantation workers in the Philippines.

Materials and Methods

Study selection. We randomly selected 88 workers, 21–53 years of age, with a 3-year history of direct or indirect exposure to EBDCs from four plantations using large amounts of dithiocarbamates for the past 20 years. The 57 directly exposed workers included mixers, assistant mixers, sprayers, flagmen, and clean-up laborers. The 31 indirectly exposed workers consisted of supervisors, maintenance crew, and research aides. The last exposure of these workers occurred between 1 and 9 days before the study was conducted. We randomly selected 43 control workers from an organic farm. These workers had no exposure to EBDCs and resided at least 50 km away from the banana plantations.

EBDCs were applied through aerial and backpack spraying on a weekly and daily basis, respectively. Other fungicides such as chlorothalonil, propanil, and bitertanol were used at the same time or interchangeably with EBDCs. The primary routes of exposure to farmers were inhalation and skin contact.

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Assessment. This cross-sectional study was conducted on 11–13 October 1999 among the EBDC-exposed workers and 7–8 December 2000 for organic-farm workers. We collected a demographic profile, nutritional history, work background, and exposure data using face-to-face interviews.

Physical examination centered on the thyroid gland. Thyroid-stimulating hormone (TSH) and free thyronine (T_4) determinations were performed using immunoradiometric assay and radioimmunoassay methods, respectively, by the Medical Research Laboratory of the Philippine General Hospital. We used the SpectraScreen TSH and T_4 assays (both from Ortho-Clinical Diagnostics, Rochester, NY, USA), which use an "antibody sandwich" method with the TSH and T_4 in the middle. The test kit can detect at least 5 µIU/mL TSH and up to 200 µIU/mL T_4. Free T_4 was determined only among subjects with elevated TSH levels. The Bureau of Research and Laboratory of the Department of Health analyzed iodine in urine using an acid-digestion method and urinary creatinine using Jaffe's reaction. The urine, blood, and environmental samples were analyzed for the presence of ETU by the Toxicology Laboratory of the Department of Pharmacology, University of the Philippines College of Medicine, using HPLC with an ultraviolet detector. A modified extraction procedure yielded a recovery rate of 90–100% ETU, with a detection limit of 0.2 ppb (Yabes A, Liwag E, Pinzon L. Unpublished data). Thyroid gland ultrasound was performed by a trained radiologist at the Tagum Regional Hospital. A fine needle aspiration biopsy was performed on subjects who had palpable nodules.

Environmental samples were collected from air through 4–8 hr continuous monitoring using 0.37-mm polyvinyl chloride filters and an air sampling device. Soil samples were collected from the top down to 0.5 m from the surface. All biologic and environmental samples were stored on dry ice and sent to the respective laboratories 24–48 hr after collection. Good laboratory practice and quality control measures were observed during the conduct of the tests.

Data analysis. Descriptive statistics, Student *t*-test, analysis of variance, Fisher's exact test, Pearson's correlation analysis, and regression analysis were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 10 (SPSS, Chicago, IL, USA).

Results

Demographic profile. The number, age, and sex of the persons examined in directly exposed, indirectly exposed, and control groups are summarized in Table 1. Despite attempts to select participants within the same age range, the exposed male workers were significantly older than their control counterparts. In general, there appeared to be a higher intake of seaweed, other seafood, and cassava among the exposed group, while the diet of the control group consisted mainly of vegetables. There was no significant difference between the two groups in the intake of fish.

Comparison of the exposed and control groups using Fisher's exact test showed no significant differences regarding history of known thyroid gland disorders and diabetes mellitus in first degree relatives ($p = 0.227$ and $p = 1.0$, respectively).

Work history and exposure. More than 83% of workers in both exposed and control groups were engaged in their particular type of work for more than 5 years and had been living in the same area during their period of employment.

Exposed workers reported handling different types of EBDCs, mostly maneb and mancozeb. It is noteworthy that 27.2% of the exposed group did not know the types of pesticides to which they were exposed. Half of those who were able to name the pesticides had been exposed to multiple chemicals. Daily utilization of personal protective equipment by workers ranged from 13.6 to 73.9%, depending on the type used. Patient records showed that almost 56% of the workers handled EBDCs on a daily to weekly basis. Many workers (43.2%) were not able to quantify the duration of their exposure.

Physical examination findings. We found enlarged thyroid glands in 17 workers from the EBDC-using plantations and only 2 among the organic-farm workers. There was no significant difference in the neck diameter of the two groups ($p = 0.07$) after controlling for variables such as age, sex, height, and weight. We found no significant difference in the physical diagnosis of goiter in the two groups for both female ($p = 0.16$) and male ($p = 0.79$) workers.

Thyroid function tests and ultrasound findings. TSH levels were higher among both types of exposed workers compared with those of organic-farm workers ($p = 0.34$) (Table 1). Compared with control values, TSH values were elevated in three exposed workers (5.1, 5.8, and 6.2 mIU/L), although their free T_4 levels were within normal limits (12.9–15.5 pMol/L). After controlling for age, we found no statistically significant difference in the TSH levels between the exposed and control groups ($p = 0.24$).

The mean level of urinary iodine among the exposed group was not significantly different from that of the control group after correcting for dietary differences ($p = 0.45$).

Nine of the exposed workers and three organic-farm workers had abnormal thyroid ultrasound results. Of the exposed workers, five showed normal-sized thyroid glands with solitary nodules. Among the control group, two had diffuse thyroid parenchymal disease and one with a small solitary nodule (Table 2). Results of the Fisher's exact test on the proportion of exposed and control farmers with abnormal thyroid ultrasound findings showed no significant difference ($p = 1.000$). Age and dietary preferences had insignificant influence on the development of goiter among the study groups at $p = 0.421$ and $p = 0.559$, respectively.

Two women with palpable nodules in the exposed group underwent fine needle aspiration biopsy, and cytology results showed colloid goiter.

Biologic and environmental monitoring. Significant differences were found in both arithmetic and geometric mean blood ETU

Table 1. Demographic profile and laboratory examinations for exposed and control workers.

Parameters	Directly exposed ($n = 57$)	Indirectly exposed ($n = 31$)	Control ($n = 43$)	*p*-Value
Age				
Mean ± SE	35.5 ± 0.88	37.8 ± 1.31	33.5 ± 1.27	0.05[a]
Range	21–50	22–53	20–50	
Sex				
Male	57	20	34	
Female	0	11	9	
Blood ETU				
Mean ± SE, ppb	4.45 ± 0.55	2.55 ± 0.60	0.30 ± 0.04	< 0.001[a]
GM (SE), ppb	2.55 (0.32)	0.98 (0.42)	0 (0.36)	< 0.001[a]
Urinary ETU				
Mean ± SE, ppb	378.34 ± 50.11	267.16 ± 69.9	26.31 ± 6.39	0.10[a]
GM (SE), ppb	94.73 (0.32)	134.21 (0.49)	14.09 (0.62)	0.10[a]
TSH[b] (mean ± SE, mIU/L)	1.79 ± 0.13	1.77 ± 0.21	1.52 ± 0.12	0.34[a]
Adjusted for age				0.24[c]
Urinary iodine/g creatinine	155.2 ± 12.25	188.08 ± 23.09	110.67 ± 4.95	< 0.001[a]
Adjusted for dietary preferences				0.45[c]
Air ETU[d] (ng/m^3)	8.8		16.17	< 0.001[e]
Soil ETU[f] (ng/g)	51.36		10.62	0.003[e]

GM, geometric mean.
[a]Analysis of variance. [b]Normal value = 0.3–5.0 mIU/L. [c]Linear regression. [d]U.S. EPA Year 2000 remediation goal for ambient air = 61 ng/m^3 (U.S. EPA 2000). [e]Independent Student *t*-test. [f]U.S. EPA Year 2000 remediation goal for industrial soil = 22,000 ng/g (U.S. EPA 2000).

levels of directly exposed, indirectly exposed, and control groups ($p \leq 0.001$). In contrast, both the arithmetic and geometric means of urinary ETU levels among the three groups were not statistically different ($p = 0.10$). When corrected for age and diet, blood ETU levels remained significantly different among the three groups ($p \leq 0.001$). Urinary ETU levels also remained insignificant after correction for age and diet ($p = 0.67$). Blood ETU correlated poorly with urinary ETU levels ($p = 0.156$, $r^2 = 0.024$).

ETU was detected in both soil and air samples from all plantations (Table 1). The Student t-test showed significant differences in the ETU levels of air and soil from the two areas ($p \leq 0.001$ and $p = 0.003$, respectively). Temperature and humidity levels in both study and control areas were not statistically different ($p = 0.09$ and $p = 0.13$, respectively).

Correlation studies. ETU in blood and urine was poorly correlated with environmental ETU levels. The same is true with urinary iodine and TSH levels. Furthermore, urinary and blood ETU levels were not correlated with TSH and time of spraying. Neither was there a relationship between TSH and spraying time. However, there was a strong correlation between the size of solitary nodules and blood ETU levels ($p = 0.001$) (Table 3).

Discussion

Investigation of TSH levels of EBDC-exposed workers has been advocated by previous studies because ETU is a known inhibitor of thyroid peroxidase activity (Hurley et al. 1998; IARC 1991; Marinovich et al. 1997; Steenland et al. 1997). The present study among banana plantation workers showed differences in TSH levels among the three study groups (directly exposed, indirectly exposed, and control). This finding is similar to those of Steenland et al. (1997), whose study involved 49 heavily exposed workers who sprayed EBDCs on tomatoes; TSH was significantly higher in the study group (2.13 ± 0.15 mIU/L) compared with the control group (1.6 ± 0.19 mIU/L), although both were within normal range (Steenland et al. 1997). In contrast to the study of Steenland et al. (1997), in the present study we did not find any correlation between age and TSH levels. Furthermore, we found no correlation between the time of exposure and TSH levels. This can be explained by the fact that workers from a number of plantations sprayed EBDCs on a daily basis, indicating continuous exposure.

The significant differences in the urinary iodine excretion levels observed among the three groups in the study can be explained primarily by the dietary preferences of these groups; these differences were no longer found after correcting for dietary preferences ($p = 0.45$). However, the increased urinary iodine excretion can be an effect of ETU, as seen in animal studies. Using rodent studies, Hurley et al. (1998) demonstrated that ETU can have the effect of inhibiting the iodide pump. The decreased iodide uptake leads to an increase in urinary iodine excretion. This may also be the explanation for the direct correlation between TSH levels and urinary iodine excretion among the workers in the study.

Because this is a cross-sectional study, it is difficult to ascertain the real prevalence of thyroid gland disorders and actual finding of clinical hypothyroidism among the workers. Because of the strenuous nature of the farmer's work and the course of the illness itself, it is possible that affected workers no longer perform these jobs. However, even if the presence of thyroid gland disorders in both exposed and control groups is not statistically different, the prevalence rates of thyroid gland disorders in these groups are higher than the national prevalence rates. The 1993 national nutrition survey of the Philippine Food and Nutrition Research Institute reported the prevalence rates of 0.2 for nodular goiters and 3.2 for diffuse goiters per 100 people in the study area (Velandria et al. 1997). This study showed a prevalence rate of 6.8/100 people for nodular goiters among exposed workers, which was three times higher than the observed prevalence rate in control workers. In contrast, the prevalence of diffuse goiters among the exposed group was lower (1.1/100 people) compared with the control group (4.5/100 people) and the national average (6.0/100 people) (Velandria et al. 1997).

Our finding of solitary nodules among the exposed group is significant because, in 95% of cases, thyroid cancer presents as a nodule or lump in the thyroid gland, usually solitary (Greenspan 1994; Studer and Gerber 1991). In a review of literature, Houeto et al. (1995) reported that a number of studies showed ETU to cause thyroid neoplasm in animals. Only one study in humans showed an increasing incidence of thyroid cancer in several geographic areas of the United States in relation to the degree of dithiocarbamate exposure, determined by sales and crop production statistics for dithiocarbamate-containing pesticides; this

Table 3. Correlation studies between urinary and blood ETU levels and environmental ETU levels, thyroid function, nodule size, and exposure history.

Parameter	r^2	p-Value
Blood ETU and air ETU	0.241	0.026
Blood ETU and soil ETU	0.244	0.024
Urinary ETU and air ETU	0.051	0.655
Urinary ETU and soil ETU	0.057	0.620
Urinary iodine and TSH	0.245	0.008
Blood ETU and TSH	0.000	0.999
Urinary ETU and TSH	0.102	0.334
Nodule size and blood ETU	0.956	0.001
Nodule size and urinary ETU	0.594	0.213
Nodule size and urinary iodine	0.759	0.080
Nodule size and TSH	0.575	0.177
Spraying time and blood ETU	0.107	0.438
Spraying time and urinary ETU	0.083	0.541
Spraying time and TSH	0.075	0.585

Table 2. Laboratory results of workers with abnormal ultrasound findings.

Subject no.	Sex/age (years)	Ultrasound findings	TSH (mIU/L)	Iodine (µg/g creatinine)	Blood ETU (ppb)	Urinary ETU (ppb)
Directly exposed workers						
1	M/21	Contracted thyroid lobe (4.4 × 1.40 × 1.3 cm)	1.80	213.94	6.73	270.42
2	M/36	Contracted thyroid lobe (5.05 × 0.95 × 1.45 cm)	1.20	209.00	2.21	117.82
3	M/21	Diffuse thyroid enlargement with solitary nodule (1.25 × 0.9 × 0.95 cm)	0.40	25.75	2.34	600.56
Indirectly exposed workers						
4	M/36	Solitary thyroid nodule (1.2 × 0.6 × 0.8 cm)	1.70	99.47	2.95	435.14
5	F/41	Multinodular goiter (1.9 × 1.4 × 1.0 cm, 4.5 × 4.2 × 3.7 cm, 1.2 × 2.1 × 0.6 cm)	0.8	No specimen	2.88	No specimen
6	F/39	Solitary thyroid nodule (2.5 × 2.0 × 1.6 cm)	2.40	No specimen	10.25	No specimen
7	M/40	Solitary thyroid nodule (1.15 × 1.05 × 0.75 cm)	1.20	26.98	< 0.1	17.08
8	F/41	Solitary thyroid nodule (0.9 × 0.65 × 0.60 cm)	0.70	92.03	1.17	91.26
9	M/45	Solitary thyroid nodule (1.10 × 0.85 × 0.45 cm)	1.0	170.0	1.17	35.75
Unexposed workers						
1	M/39	Diffuse thyroid parenchymal disease (Rt, 5.25 cm, Lt, 5.40 cm)	1.20	81.83	0.43	< 0.1
2	F/32	Small solid solitary nodule (0.8 × 0.4 × 0.7 cm)	2.10	98.11	< 0.1	24.76
3	F/46	Diffuse thyroid parenchymal disease (Rt, 7.10 cm, Lt, 6.45 cm)	0.90	116.83	< 0.1	65.84

Abbreviations: F, female; Lt, left; M, male; Rt, right.

is unlike the present study in which we used biomarkers of exposure. Thus, it is important that workers with thyroid gland disorders are monitored regularly for the development of cancer in later years.

All results of environmental monitoring in the present study were below the U.S. Environmental Protection Agency (EPA) guidelines for remediation for industries (U.S. EPA 2000). The air ETU values were much lower than findings in previously published studies in which ambient air monitoring of ETU during spraying of EBDCs revealed levels ranging from 400 to 5,200 ng/m^3 (Kurttio et al. 1990a, 1990b). Likewise, air monitoring done in an industrial formulating plant in Italy showed ETU levels ranging from 200 to 1,300 ng/m^3 (Aprea et al. 1998). Two factors that may account for this difference are the time of monitoring in relation to spraying and the prevailing meteorologic conditions. In these previous studies (Aprea et al. 1998; Kurttio et al. 1990a, 1990b), ambient air monitoring was conducted while the workers were spraying. In the present study, environmental monitoring was done 1–9 days after spraying.

In the present study, soil ETU levels were higher on the banana plantations than on the organic farm, which we attribute to EBDC use. The elevated air ETU and the presence of ETU in the soil on the organic farm are possibly due to spray drift coming from an adjacent plantation as enhanced by prevailing metereologic conditions.

The present study revealed generally higher levels of urinary ETU (mean, 244.01 ppb) among backpack sprayers with an acute exposure to EBDCs as well as chronic exposure for at least 3 years. Previous studies showed varying levels of urinary ETU among farmers using EBDCs (Aprea et al. 1996, 1998; Kurttio et al. 1990a, 1990b; Steenland et al. 1997). In their study among potato field applicators, Kurttio et al. (1990b) showed levels ranging between < 0.20 and 23.00 ppb after a 4-hr single exposure to EBDCs using a tractor-pulled, pump-operated spray. In contrast, Steenland et al. (1997) showed mean urinary ETU levels of 58 ppb among 49 applicators. The difference in the recovery rate of the HPLC procedure [50% for Kurttio et al. (1990b) and 92% for this study] and the difference in the limit of detection [10 ppb for Steenland et al. (1997) and 0.2 ppb for our study) could account for the higher urinary ETU levels observed among Filipino workers. To provide more evidence for this assumption, it is necessary to quantify the EBDC exposure of farmers into milligrams per kilogram per day. The presence of urinary ETU among the organic-farm workers can be explained by exposure from nearby plantations that use aerial spraying and also by possible use of pesticides by neighbors.

Kurttio et al. (1990b) stated that urinary ETU is not the ideal choice for biologic monitoring of EBDC or ETU exposure because of ETU's biological properties and because of the complexity of the biotransformation of EBDC to ETU. In this study we showed blood ETU levels to be significantly elevated among the directly exposed farmers compared with the indirectly exposed and control groups. This relationship was not demonstrated by urinary ETU levels among the three groups. Furthermore, urinary ETU levels poorly correlated with blood ETU levels. Therefore, blood ETU levels may be a better biomarker than urinary ETU for monitoring exposure to EBDCs.

The significant elevation of ETU in urine and blood and low environmental ETU levels indicate that the exposure of the workers to ETU was mainly from the direct handling of EBDCs rather than from ambient air. This is supported by the finding of no correlation between blood and urinary ETU levels and environmental ETU levels.

Although blood ETU levels decrease several days after cessation of exposure to EBDCs and the half-life of ETU is approximately 28 days, the daily exposure of farmers in this study through backpack spraying and weekly exposure through aerial spraying creates a steady-state concentration of ETU in the blood. The persistently high levels of ETU in the blood can increase the likelihood for the rapid growth of the thyroid nodule. This can explain the strong direct correlation between the size of thyroid nodules and blood ETU levels. With increasing size of the nodule (> 4 cm), there is a greater chance for the nodule developing into cancer. The assumption of persistently high blood ETU levels in the workers should be confirmed by collecting repeated samples over several months.

Conclusions

In this study we did not find significant differences in thyroid function tests of exposed and control groups after controlling for age and dietary preferences. However, we found a higher prevalence of solitary nodules in exposed workers as detected by ultrasound. Furthermore, findings showed that soil and ambient air ETU levels were below the U.S. EPA remediation levels (U.S. EPA 2000). Blood ETU levels were significantly higher among the exposed group compared with the control group; this test is a more reliable biomarker for EBDC exposure than urinary ETU. Also, the size of the thyroid nodule is strongly correlated with blood ETU level.

Health monitoring of individuals exposed to EBDCs should include checking for thyroid gland disorders, particularly nodular goiters. We recommend that blood ETU levels be determined on workers who are directly exposed to EBDCs. Workers with solitary nodules should be followed closely to rule out the possibility of thyroid cancer.

References

Aprea C, Betta A, Catenacci G, Lotti A, Minoia C, Passini W, et al. 1996. Reference values of urinary ethylenethiourea in four regions of Italy (multicentric study). Sci Total Environ 192:83–93.

Aprea C, Sciarra G, Sartorelli P, Mancini R, Di Luca V. 1998. Environmental and biological monitoring of exposure to mancozeb, ETU and dimethoate during industrial formulation. J Toxicol Environ Health 53:263–281.

Blackwell-Smith R Jr, Finnegan JK, Larson PS, Sahyoun PF, Dreyfuss ML, Haag HB. 1953. Toxicologic studies on zinc and disodium ethylenebisdithiocarbamates. J Pharmacol Exp Ther 109:159–166.

Brucker-Davis F. 1998. Effects of environmental synthetic chemicals on thyroid function. Thyroid 8:827–856.

FAO/WHO. 1965. Evaluation of the Toxicity of Pesticide Residues in Food. FAO Meeting Report No. PL:1965/10/1; WHO/Food Add/27.65. Geneva:World Health Organization.

———. 1971. 1970 Evaluations of Some Pesticide Residues in Food. ACP 1979/M/12/1; WHO/Food Add/71.42. Geneva:World Health Organization.

Greenspan FS. 1994. The thyroid gland. In: Basic and Clinical Endocrinology (Greenspan FS, Baxter JD, eds). Norwalk, CT:Appleton and Lange, 216–217.

Houeto P, Bindoula G, Hoffman JR. 1995. Ethylenebisdithiocarbamates and ethylenethiourea: possible human health hazards. Environ Health Perspect 103:568–573.

Hurley PM, Hill RN, Whiting RJ. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ Health Perspect 106:437–445.

IARC. 1991. Fungicides. IARC Monogr Eval Carcinog Risks Hum 53:403–422.

International Programme on Chemical Safety. 1988. Dithiocarbamate Pesticides, Ethylenethiourea, and Propylenethiourea: A General Introduction. Environmental Health Criteria 78. Geneva:World Health Organization. Available: http://www.inchem.org/documents/ehc/ehc/ehc78.htm [accessed 18 November 2003].

Kato Y, Odanaka Y, Teramoto S, Matano O. 1976. Metabolic fate of ethylenethiourea in pregnant rats. Bull Environ Contam Toxicol 16(5):546–555.

Kurttio P, Vartiainen T, Savolainen K. 1990a. Environmental and biological monitoring of exposure to ethylenebisdithiocarbamate fungicides and ethylenethiourea. Br J Ind Med 47:203–206.

———. 1990b. Ethylene thiourea in air and in urine as an indicator of exposure to ethylenebisdithiocarbamate fungicides. Scand J Work Environ Health 16:203–207.

Marinovich M, Guizzetti M, Ghilardi F, Viviani B, Corsini E, Galli CL. 1997. Thyroid peroxidase as toxicity target for dithiocarbamates. Arch Toxicol 71:508–512.

Newsome WH. 1974. The excretion of ethylenethiourea by rat and guinea pig. Bull Environ Contam Toxicol 11:174–176.

Ruddick JA, Williams DT, Hierlihy L, Khera KS. 1976. ^{14}C-Ethylenethiourea: distribution, excretion, and metabolism in pregnant rats. Teratology 13:263–266.

Seifter J, Ehrich WE. 1948. Goitrogenic compounds: pharmacological and pathological effects. J Pharmacol Exp Ther 92:303–314.

Smith DM. 1984. Ethylene thiourea: thyroid function in two groups of exposed workers. Br J Ind Med 41:362–366.

Steenland K, Cedillo L, Tucker J, Hines C, Sorensen K, Deddens J, et al. 1997. Thyroid hormones and cytogenetic outcomes in backpack sprayers using ethylenebis(dithiocarbamate) (EBDC) fungicides in Mexico. Environ Health Perspect 105:1126–1130.

Studer H, Gerber H. 1991. Clinical manifestations and management of non-toxic diffuse and nodular goiter. In: Werner and Ingbar's The Thyroid: A Fundamental and Clinical Test (Braverman LE, Utiger RD, eds). 6th ed. Philadelphia:Lippincott, 1130–1132.

U.S. EPA. 2000. EPA Region IX Preliminary Remediation Goal (PRG) Tables. 2000 Update. San Francisco, CA:U.S. Environmental Protection Agency Region 9.

Velandria FV, Magbitang JA, Tanchoco CC, Mendoza TS, Orense CL, Tangco JB, et al. 1997. Fourth national nutrition survey, Philippines, 1993. Philipp J Nutr 44:49–65.